

Clostridium difficile-associated Disease in the Elderly, United States

To the Editor: Zilberberg et al. (1) recently commented on the increase of hospitalizations for *Clostridium difficile*-associated disease (CDAD) and noted an increase in the case-fatality rate during 2000–2005. These findings refer to the entire US adult population and agree with our observations for the elderly (≥ 65 years of age). We assessed trends of CDAD in the elderly by using hospital billing data from the Centers for Medicare and Medicaid Services (CMS), which covers 98% of the elderly population (2). We abstracted all 1,054,125 hospitalization records that included *C. difficile* (International Classification of Diseases, 9th revision, Clinical Modification [ICD 9-CM], diagnosis code 008.45) in any of the 10 diagnosis code positions for a 14-year period (1991–2004). We used elderly-population data from the 1990 and 2000 US Census. The ICD code for *C. difficile* was introduced in 1992. Case-patients in our dataset prior to this date represent severe illness and were hospitalized for >1 year and therefore were still in the hospital when the ICD code was introduced. We considered data from 1993 through 2004 because 1991 and 1992 are not representative due to introduction of the ICD code.

We observed an increase in overall hospitalizations that included a diagnosis for CDAD (online Appendix Figure, panel A, available from www.cdc.gov/EID/content/15/2/343-appF.htm) and an increase in rates of CDAD from 13.71/10,000 elderly in 1993 to 38.78/10,000 in 2004 (3). The highest rate of hospitalizations was detected in the oldest patients (≥ 85 years of age), 48.2/10,000 vs. 11.9 in those 65–74 years of age and 26.0 in those 75–84 years of age (3). These rates might be

higher than rates reported by Zilberberg et al. because our records account for all treated conditions recorded by all 10 diagnosis codes. The ICD code for CDAD typically does not appear in the primary and secondary diagnosis; overall, 60% of all CMS records list CDAD as codes 3–10 (3). Primary and secondary codes typically represent diagnoses for which the patient is admitted, whereas diagnosis codes 3–10 are codes used for chronic conditions and sequelae. The online Appendix Figure, panel A, shows the change in the proportion of CDAD cases in each diagnosis code over the study period. The proportion of CDAD in the primary and secondary diagnosis position increased during 1996–1997; however, this proportion is stabilizing at $\approx 25\%$.

Zilberberg et al. observed a doubling in age-adjusted case-fatality rates from 1.2% in 2000 to 2.2% in 2004 (1), which is an annual increase of 0.2% over the 5-year period. We are not able to calculate case-fatality rate by using CMS data because these data do not provide cause of death, only an indicator of whether the patient died during that hospital stay. However, we observed an increase in the percentage of patients with CDAD who died, from 8.8% in 1993 to 9.7% in 2004, which is an annual increase of 0.075% over the 12-year period. We also observed a peak in 2000; 10.4% of patients with CDAD died. This peak is unusual and unexplained and requires further analysis. Data on deaths must be interpreted with caution because they may be affected by severe conditions and age (oldest patients).

We observed an increasing trend and strong seasonal pattern in CDAD hospitalizations. The online Appendix Figure, panel B, shows this seasonal pattern by week during 1993–2004. This figure shows an increasing trend over time with a sharp change in slope in 2001. This increasing trend may represent an increase in disease or may be caused by increased testing

and recognition of disease. Diagnosis of CDAD in the United States is now made by using an enzyme immunoassay that is relatively easier and cheaper to perform than a cytotoxin assay (4), which may account for the increased trend.

Increases in rates of CDAD may be caused by a reporting bias of gastroenteric diseases (5–7). To assess this possibility, we extracted all records that included other infectious gastroenteritis without CDAD (all other gastrointestinal [GI] infections, ICD 001–009 without 008.45) and compared the trend with CDAD hospitalizations (online Appendix Figure, panel B). The online Appendix Figure shows that rates for all other GI infections remained fairly constant over the study period, and a reporting bias for GI infections does not account for the ≈ 3 -fold increase in CDAD hospitalizations. CDAD hospitalization rates for the elderly also show a strong annual seasonal pattern (online Appendix Figure, panel B), which was estimated to peak in the second week of March, the 10th week of the year. This seasonality suggests dominant routes of transmission that may be environmentally driven.

Our findings support the observations of Zilberberg et al. and demonstrate the substantial increase in CDAD-related hospitalizations over time. These findings and the aging population in the United States underscore the need for further research to understand all aspects of CDAD.

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Letters

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Viral Etiology of Common Cold in Children, Finland

To the Editor: The common cold is regarded as a viral disease. In the first years of the 21st century, several new respiratory viruses have been identified, such as human metapneumovirus (hMPV), coronaviruses NL63 and HKU1, and human bocavirus (HBoV). Many studies have addressed the role of these viruses in hospital settings, but few studies have been conducted among outpatients. We examined the etiology of the common cold in young children who were newly symptomatic but had no need of hospital care. We hypothesized that the etiology could be detected in all cases by using modern diagnostics that test for 16 viruses in outpatients.

Between February 1996 and April 1998, we collected nasopharyngeal aspirate samples in an outpatient setting from 194 Finnish children having newly onset (<48 h) symptoms of common cold but no acute otitis media (AOM) or other symptoms demanding antimicrobial therapy (1). The mean age of the study population was 2.1 years (range 0.7–3.9 years), and 81% attended day care. The parents of all participants gave written informed consent, and the study protocol was approved by the Ethics Committee of Turku University Hospital in Turku, Finland.

The nasopharyngeal aspirate samples were processed freshly for antigen detection (respiratory syncytial virus [RSV]; parainfluenza viruses 1, 2, and 3; influenza A and B viruses; and adenovirus) by time-resolved fluoroimmunoassay (2). Stored samples were subjected to nucleic acid testing (NAT) for picornaviruses; RSV; coronaviruses 229E, OC43, NL63, and HKU1; influenza C virus; HBoV; hMPV; and adenovirus. Recently, these samples were reanalyzed for rhinovirus and enterovirus using real-

time PCR for the amplification step (1,3–6).

At least 1 respiratory virus was detected in 179 (92%) of 194 children. Rhinovirus was the most common respiratory virus, found in 138 (71%) children (Table). Other viruses were found in varying proportions: HBoV was present in 27 (14%) children; adenovirus was found in 23 (12%) (3 were positive by antigen detection, and 23 by NAT); enterovirus was present in 20 (10%); coronaviruses were found in 11 (6%) (NL63:7; HKU1:2; 229E/OC43:2); influenza viruses were present in 11 (6%) (A:4; B:1; C:6); RSV was shown in 8 (4%) (all were positive by antigen detection and NAT); parainfluenza viruses were present in 7 (4%) (1:1; 3:6); and hMPV was found in 3 (2%). The Table shows the concomitant occurrence of all viruses. Among children with a positive viral finding, 46 (26%) had 2 viruses, and 10 (6%) had 3 or 4 viruses concomitantly. The viruses occurring most frequently with other viruses were adenovirus (100%), HBoV (81%), and enterovirus (75%).

Although our diagnostic panel was incomplete, lacking parechoviruses and parainfluenza type 4 virus, we detected ≥1 respiratory viruses in 92% of the children who had a common cold. As expected, rhinovirus was the leading cause of the common cold in these children. The role of picornaviruses was also emphasized by the abundance of enteroviruses. Enterovirus has gained attention mainly in severe infections, e.g., meningoencephalitis, and is rarely included in diagnostics for respiratory infections. However, PCR has shown that enterovirus commonly causes upper and lower respiratory infections that may be complicated by AOM or expiratory wheezing (4,7). Thus, enterovirus should be included in the diagnostic panels of respiratory infections. HBoV was the second most prevalent virus in our study population. Since its discovery in 2005, HBoV positivity has been